REMARKS

After entry of the above amendments, claims 27-44 and 46 are the claims remaining in this application.

Amendments

The specification has been amended to update the status of related applications, correct obvious typographical errors in reference citations in the background section, and correct other obvious typographical errors, as well as to add a new sequence listing number 51 for a sequence that obviously should have a new number and to change the sequences for SEQ ID NOS:1, 3, 7, 8, 10, and 30, as explained below.

Claims 1-26, 45 and 47-51 are canceled, without intention either to acquiesce in the rejection or abandon the subject matter contained therein, and without prejudice to filing a divisional application based thereon.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**."

For the Examiner's convenience, a clean copy of the currently pending claims is attached hereto.

It is believed that the now-pending claims are in condition for allowance based on the foregoing submissions. If the Examiner has any questions regarding this response, the Examiner is invited to call the undersigned at the number indicated below.

Respectfully submitted,
GENENTECH, INC.

Date: Feb. 20, 2001 By: Janet E. Hasak

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PATENT TRADEMARK OFFICE

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

1. Paragraph beginning at first line of page 1 (first two paragraphs on page 1) (the original and the one introduced by the transmittal form) has been amended as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

This is a continuation of co-pending application[~~(s) Serial Number~~] **U.S. Ser. No.** 09/337,227 filed [~~on~~] June 22, 1999, which is a continuation-in-part **application** of **co-pending** [~~application Serial No.~~] **U.S. Ser. No.** 09/052,888[~~,~~] filed March 31, 1998, **now U.S. Pat. No. 6,251,865,** which is a continuation-in-part **application** of [~~application Serial Number~~] **U.S. Ser. No.** 08/825,852[~~,~~] filed April 4, 1997, issued as U.S. Patent Number 6,121,416, which applications are incorporated herein by reference and to which applications priority is claimed under 35 USC §120.

[~~This application is a continuation-in-part application of co-pending U.S. Ser. No. 09/052,888 filed March 31, 1998, which is a continuation-in-part application of co-pending U.S. Ser. No. 08/825,852 filed April 4, 1997, which applications are incorporated herein by reference and to which applications priority is claimed under 35 USC §120.~~]

2. Paragraph beginning at line 4 of page 2 has been amended as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

Like GH, IGF-I is a potent anabolic protein. See Tanner *et al.*, Acta Endocrinol., 84: 681-696 (1977); Uthne *et al.*, J. Clin. Endocrinol. Metab., 39: 548-554 (1974). See also Ross *et al.*, Intensive Care Med., 19 Suppl. 2: S54-57 (1993), which is a review of the role of insulin, GH, and IGF-I as anabolic agents in the critically ill. IGF-I has hypoglycemic effects similar to those of insulin, but also promotes positive nitrogen balance (Underwood *et al.*, Hormone Res.,

24: 166 (1986); Guler *et al.*, N. Engl. J. Med., 317: 137 (1987)). Due to this range of activities, IGF-I is being tested in humans for such widely disparate uses as wound healing, treatment of diabetes, reversal of whole body catabolic states, treatment of heart conditions such as congestive heart failure, and treatment of neurological disorders (Guler *et al.*, Proc. Natl. Acad. Sci. USA, 85: 4889-4893 (1988); Duerr *et al.*, J. Clin. Invest., 95: 619-627 (1995); and **Barinaga,** Science, 264: 772-774 (1994)).

3. Paragraph beginning at line 7 of page 5 has been amended as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

The administration of rhIGF-I to Type II diabetics, as reported by Schalch *et al.*, J. Clin. **Endo.** Metab., 77: 1563-1568 (1993), demonstrated a fall in both serum insulin as well as a paralleled decrease in C peptide levels. This indicated a reduction in pancreatic insulin secretion after five days of IGF-I treatment. This effect has been independently confirmed by Froesch *et al.*, Horm. Res., 42: 66-71 (1994). *In vivo* studies in normal rats also illustrate that IGF-I infusion inhibits pancreatic insulin release (Fur**n**sinn *et al.*, Endocrinology, 135: 2144-2149 (1994)). In addition, in pancreas perfusion preparations, IGF-I also suppressed insulin secretion (Leahy *et al.*, Endocrinology, 126: 1593-1598 (1990)). Despite these clear *in vivo* inhibitory effects of IGF-I on insulin secretion in humans and animals, *in vitro* studies have not yielded such uniform results.

4. Paragraph beginning at line 21 of page 5 has been amended as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

RhIGF-I has the ability to improve insulin sensitivity. For example, rhIGF-I (70 μg/kg bid) improved insulin sensitivity in non-diabetic, insulin-resistant patients with myotonic dystrophy (Vlachopapadopoulou *et al.*, J. Clin. Endo. Metab., [~~12~~] **80**: 3715-3723 (1995)). Saad

et al., Diabetologia, 37: Abstract 40 (1994) reported dose-dependent improvements in insulin sensitivity in adults with obesity and impaired glucose tolerance following 15 days of rhIGF-I treatment (25 μg and 100 μg/kg bid). RhIGF-I also improved insulin sensitivity and glycemic control in some patients with severe type A insulin resistance (Schoenle *et al.*, Diabetologia, 34: 675-679 (1991); Morrow *et al.*, Diabetes, 42 (Suppl.): 269 (1993) (abstract); Kuzuya *et al.*, Diabetes, 42: 696-705 (1993)) and in other patients with non-insulin dependent diabetes mellitus (Schalch *et al.*, "Short-term metabolic effects of recombinant human insulin-like growth factor I (rhIGF-I) in type II diabetes mellitus", in: Spencer EM, ed., Modern Concepts of Insulin-like Growth Factors (New York: Elsevier: 1991) pp. 705-71[~~5~~]**3**; Zenobi *et al.*, J. Clin. Invest., 90: 2234-2241 (199[~~3~~]**2**)).

5. Paragraph beginning at line 12 of page 6 has been amended as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

A general scheme for the etiology of some clinical phenotypes that give rise to insulin resistance and the possible effects of administration of IGF-I on selected representative subjects is given in several references. See, *e.g.*, Elahi *et al.*, "Hemodynamic and metabolic responses to human insulin-like growth factor-1 (IGF-I) in men," in: Modern Concepts of Insulin-Like Growth Factors, (Spencer, EM, ed.), Elsevier, New York, pp. 219-224 (1991); Quin[~~n~~] *et al.*, New Engl. J. Med., 323: 1425-1426 (1990); Schalch *et al.*, "Short-term metabolic effects of recombinant human insulin-like growth factor 1 (rhIGF-I) in type 11 diabetes mellitus," in: Modern Concepts of Insulin-Like Growth Factors, (Spencer, EM, ed.), Elsevier, New York, pp. 705-71[**4**]**3** (1991); Schoenle *et al.*, Diabetologia, 34: 675-679 (1991); Usala *et al.*, N. Eng. J. Med., 327: 853-857 (1992); Lieberman *et al.*, J. Clin. Endo. Metab., 75: 30-36 (1992); Zenobi *et al.*, J. Clin. Invest., 90: 2234-2241 (1992); Zenobi *et al.*, J. Clin. Invest., 89: 1908-1913 (1992); Kerr *et al.*, J. Clin. Invest., 91: 141-147 (1993). When IGF-I was used to treat Type II diabetic patients in the clinic at a dose of 120-160 μg/kg twice daily, the side effects outweighed the

benefit of the treatment (Jabri *et al.*, Diabetes, 43: 369-374 (1994)). See also Wilton, Acta Paediatr., 383: 137-141 (1992) regarding side effects observed upon treatment of patients with IGF-I.

6. Paragraph beginning at line 25 of page 14 has been amended as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

Accordingly, the present invention relates, in a first embodiment, to a peptide comprising the following sequence:

$Xaa_{(1-4)}CysXaa_{(6)}Xaa_{(7)}GlyXaa_{(9)}$[~~Leu~~]**Xaa**$_{(10)}Xaa_{(11)}Xaa_{(12)}$[~~Leu~~]**Xaa**$_{(13)}CysXaa_{(15)}$ $Xaa_{(16)}Xaa_{(17)}Xaa_{(18)}$ (SEQ ID NO:1), wherein $Xaa_{(1-4)}$ is absent or is between 1 and 4 amino acids of any kind, $Xaa_{(6)}$, $Xaa_{(7)}$, $Xaa_{(9)}$, $Xaa_{(11)}$, $Xaa_{(15)}$, and $Xaa_{(16)}$ are independently any amino acid, **Xaa $_{(10)}$ and Xaa$_{(13)}$ are independently Leu or Nle,** and $Xaa_{(12)}$, $Xaa_{(17)}$, and $Xaa_{(18)}$ are independently Nal(1), His, Phe, Trp, Tyr, Pro, Gln, or Met.

7. Paragraph beginning at line 12 of page 15 has been amended as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

In another preferred embodiment, this peptide comprises the following sequence:

$CysXaa_{(6)}Xaa_{(7)}GlyXaa_{(9)}$[~~Leu~~]**Xaa**$_{(10)}Xaa_{(11)}Trp$[~~Leu~~]**Xaa**$_{(13)}CysXaa_{(15)}Xaa_{(16)}Xaa_{(17)}$ $Xaa_{(18)}$ (SEQ ID NO:3). More preferably, such peptide comprises one of the following sequences:

CysArgAlaGlyAlaLeuGlnTrpLeuCysGluLysTyrPhe (SEQ ID NO:4);

CysArgAlaGlyArgLeuGlnTrpLeuCysGluLysTyrPhe (SEQ ID NO:5);

CysArgAlaGlyAsnLeuGlnTrpLeuCysGluLysTyrPhe (SEQ ID NO:6);

CysArgAlaGlyPro[~~Leu~~]**Nle**GlnTrpLeuCysGluLysTyrPhe[~~, where the first Leu is Nle~~] (SEQ ID NO:7);

CysArgAlaGlyProLeuGlnTrp[~~Leu~~]**Nle**CysGluLysTyrPhe[~~, where the second Leu is Nle~~] (SEQ ID NO:8);
CysArgAlaGlyProLeuGlnArgLeuCysGluLysTyrPhe (SEQ ID NO:9);
CysArgAlaGlyProLeuGln[~~Ala~~]**Nal(1)**LeuCysGluLysTyrPhe[~~, where the second Ala is Nal(1)~~] (SEQ ID NO:10); or
CysArgAlaGlyProLeuGlnHisLeuCysGluLysTyrPhe (SEQ ID NO:11).

8. Paragraph beginning at line 1 of page 18 has been amended as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

In another aspect of the invention, the above peptide having SEQ ID NO:1 or SEQ ID NO:3 has a C-terminal fusion comprising the following sequence:
GlyGlyGlySerGlyGlyAlaGlnHisAspGluAlaValAspAsnLysPheAsnLysGluGlnGlnAsn AlaPheTyrGlu[~~Iso~~]**Ile**LeuHisLeuProAsnLeuAsnGluGluGlnArgAsnAlaPhe[~~Iso~~] **Ile**GlnSerLeuLysAspAspProSerGlnSerAlaAsnLeuLeuAlaGluAlaLysLysLeuAsnAspAlaGlnAlaProAsnValAspMetAsn (SEQ ID NO:30).

9. Paragraph beginning at line 20 of page 29 has been amended as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

A "disorder" is any condition that would benefit from treatment with an IGF, including but not limited to, for example, lung diseases, hyperglycemic disorders as set forth below, renal disorders, such as acute and chronic renal insufficiency, end-stage chronic renal failure, glomerulonephritis, interstitial nephritis, pyelonephritis, glomerulosclerosis, *e.g.,* Kimmelstiel-Wilson in diabetic patients and kidney failure after kidney transplantation, obesity, GH-insufficiency, Turner's syndrome, Laron's syndrome, short stature, undesirable symptoms associated with aging such as obesity and increased fat mass-to-lean ratios, immunological

disorders such as immunodeficiencies including decreased CD4 counts and decreased immune tolerance or chemotherapy-induced tissue damage, bone marrow transplantation, diseases or insufficiencies of cardiac structure or function such as heart ~~[disfunctions]~~ **dysfunctions** and congestive heart failure, neuronal, neurological, or neuromuscular disorders, *e.g.,* peripheral neuropathy, multiple sclerosis, muscular dystrophy, or myotonic dystrophy, and catabolic states associated with wasting caused by any condition, including, *e.g.,* trauma or wounding or infection such as with a bacterium or human virus such as HIV, wounds, skin disorders, gut structure and function that need restoration, and so forth. The disorder being treated may be a combination of two or more of the above disorders. The preferred disorders targeted for treatment herein are diabetes and obesity, heart ~~[disfunctions]~~ **dysfunctions**, kidney disorders, neurological disorders, whole body growth disorders, and immunological disorders.

10. Paragraph beginning at line 10 of page 42 has been amended as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

The present invention relates to various classifications of peptides having the function of displacing IGFBP-1. In one embodiment, the peptide comprises the following sequence: $Xaa_{(1-4)}CysXaa_{(6)}Xaa_{(7)}GlyXaa_{(9)}$~~[Leu]~~**Xaa**$_{(10)}Xaa_{(11)}Xaa_{(12)}$~~[Leu]~~**Xaa**$_{(13)}CysXaa_{(15)}$ $Xaa_{(16)}Xaa_{(17)}Xaa_{(18)}$ (SEQ ID NO:1), wherein $Xaa_{(1-4)}$ is absent or is between 1 and 4 amino acids of any kind, $Xaa_{(6)}$, $Xaa_{(7)}$, $Xaa_{(9)}$, $Xaa_{(11)}$, $Xaa_{(15)}$, and $Xaa_{(16)}$ are independently any amino acid, **Xaa $_{(10)}$ and Xaa$_{(13)}$ are independently Leu or Nle,** and $Xaa_{(12)}$, $Xaa_{(17)}$, and $Xaa_{(18)}$ are independently Nal(1), His, Phe, Trp, Tyr, Pro, Gln, or Met.

11. Paragraph beginning at line 19 of page 42 has been amended as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

Preferably, in ~~[formula (A)]~~ **SEQ ID NO:1** above, $Xaa_{(1-4)}$, $Xaa_{(6)}$, $Xaa_{(7)}$, $Xaa_{(9)}$, $Xaa_{(11)}$, $Xaa_{(15)}$, and $Xaa_{(16)}$ are independently Ala, Leu, [~~Iso~~] **Ile**, Glu, Arg, Val, Gly, Gln, Ser, Met, Pro, Thr, Asn, Lys, or Trp, more preferably Ala, Glu, Arg, Val, Gly, Gln, Ser, Pro, Asn, or Lys. Independently, or in combination with this, preferably $Xaa_{(12)}$, $Xaa_{(17)}$, and $Xaa_{(18)}$ are independently Phe, Trp, Tyr, Pro, Gln, or Met, more preferably Phe, Trp, or Tyr, and most preferably Phe or Trp. Independently, or in combination with this, $Xaa_{(9)}$ is Ala, Arg, Asn, or Pro. In more preferred embodiments, $Xaa_{(6)}$ is Arg, $Xaa_{(7)}$ is Ala, $Xaa_{(9)}$ is Pro, $Xaa_{(11)}$ is Gln, $Xaa_{(12)}$ is Trp, $Xaa_{(15)}$ is Glu, $Xaa_{(16)}$ is Lys, $Xaa_{(17)}$ is Tyr, and/or $Xaa_{(18)}$ is Phe.

12. Paragraph beginning at line 7 of page 43 has been amended as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

Another preferred set of peptides comprising SEQ ID NO:1 is $CysXaa_{(6)}Xaa_{(7)}GlyXaa_{(9)}$[~~Leu~~]**$Xaa_{(10)}$**$Xaa_{(11)}Trp$[~~Leu~~]**$Xaa_{(13)}$**$CysXaa_{(15)}Xaa_{(16)}Xaa_{(17)}Xaa_{(18)}$ (SEQ ID NO:3). More specifically preferred such peptides comprise one of the following sequences: SEQ ID NO:4, 5, 6, 7, 8, 9, 10, or 11.

13. Paragraph beginning at line 22 of page 43 has been amended to form two paragraphs as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

The most preferred of those peptides comprising SEQ ID NO:1 comprise one of the following sequences: SEQ ID NO:4, 5, 6, 7, 8, 9, 10, 11, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29.

In another preferred aspect, the peptide comprising SEQ ID NO:1 has a C-terminal fusion (e.g., a sequence attached to C-terminal residue $Xaa_{(18)}$) comprising the following sequence:

GlyGlyGlySerGlyGlyAlaGlnHisAspGluAlaValAspAsnLysPheAsnLysGluGlnGlnAsn AlaPheTyrGlu[~~Iso~~]**Ile**LeuHisLeuProAsnLeuAsnGluGluGlnArgAsnAlaPhe[~~Iso~~] **Ile**GlnSerLeuLysAspAspProSerGlnSerAlaAsnLeuLeuAlaGluAlaLysLysLeuAsnAspAlaGlnAlaP roAsnValAspMetAsn (SEQ ID NO:30).

14. Paragraph beginning at line 22 of page 44 has been amended as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

In another embodiment, the invention provides a peptide comprising the following sequence:

$Xaa_{(1-4)}Xaa_{(5)}Xaa_{(6-7)}$ProLeuGlu$Xaa_{(11)}$LeuAla$Xaa_{(14)}Xaa_{(15)}Xaa_{(16)}Xaa_{(17)}GluXaa_{(19)}$ (SEQ ID NO:32), wherein $Xaa_{(1-4)}$ is absent or is between 1 and 4 amino acids of any kind; $Xaa_{(5)}$ is any amino acid, $Xaa_{(6-7)}$ is absent or is between 1 and 2 amino acids, $Xaa_{(14)}$ and $Xaa_{(15)}$ are independently any amino acid, $Xaa_{(11)}$ and $Xaa_{(16)}$ are independently Nal(1), His, Phe, Trp, Tyr, Pro, Gln, or Met, $Xaa_{(17)}$ is absent or is [~~1-napthyl-Ala~~]**Nal(1)**, His, Phe, Trp, Tyr, Pro, Gln, or Met, and $Xaa_{(19)}$ is absent or is Gly.

15. Paragraph beginning at line 5 of page 85 has been amended as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

With regard to construction of the delivery device, any form of aerosolization known in the art, including but not limited to nebulization, atomization, or pump aerosolization of a liquid formulation, and aerosolization of a dry powder formulation, can be used in the practice of the invention. A delivery device that is uniquely designed for administration of solid formulations is envisioned. Often, the aerosolization of a liquid or a dry powder formulation will require a propellent. The propellent may be any propellant generally used in the art. Specific nonlimiting examples of such useful propellants include a [~~chlorofluorocarbon~~] **chlorofluorocarbon**, a

hydrofluorocarbon, a ~~[hydochlorofluorocarbon]~~ **hydrochlorofluorocarbon**, or a hydrocarbon, including ~~[triflouromethane]~~ **trifluoromethane**, ~~[dichlorodiflouromethane]~~ **dichlorodifluoromethane**, ~~[dichlorotetrafuoroethanol]~~ **dichlorotetrafluoroethanol**, and ~~[1,1,1,2-tetraflouroethane]~~ **1,1,1,2-tetrafluoroethane**, or combinations thereof.

16. Paragraph beginning at line 20 of page 86 has been amended as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

The liquid aerosol formulation may include a carrier. The carrier is a macromolecule that is soluble in the circulatory system and that is physiologically acceptable where physiological acceptance means that those of skill in the art would accept injection of said carrier into a patient as part of a therapeutic regime. The carrier preferably is relatively stable in the circulatory system with an acceptable plasma half life for clearance. Such macromolecules include but are not limited to soya lecithin, oleic acid, and ~~[sorbetan]~~ **sorbitan** trioleate, with sorbitan trioleate preferred.

17. Paragraph beginning at line 22 of page 96 has been amended as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

W8 was also completely conserved in IGFBP-1 selected peptide-phage libraries, although the alanine substitution had a smaller effect on binding than in the case of L6 or L9. Therefore, several large side-chain substitutions were tested at this position. Interestingly, arginine, 1-naphthylalanine (Nal(1)), or histidine substitutions (bp1-22, bp1-23, and bp1-24, respectively) each had modest (<10-fold) effects on IGFBP-1 binding affinity (Table I). From these experiments, a new consensus sequence for IGFBP-1 binding may be formulated as follows: $CysXaa_{(6)}Xaa_{(7)}GlyXaa_{(9)}$~~[Leu]~~**Xaa**$_{(10)}Xaa_{(11)}Trp$~~[Leu]~~**Xaa**$_{(13)}CysXaa_{(15)}Xaa_{(16)}Xaa_{(17)}Xaa_{(18)}$ (SEQ ID NO:3), where $Xaa_{(6)}$, $Xaa_{(7)}$, $Xaa_{(9)}$, $Xaa_{(11)}$, $Xaa_{(15)}$, and $Xaa_{(16)}$ are independently any amino

acid, **Xaa$_{(10)}$ and Xaa$_{(13)}$ are independently Leu or Nle,** and Xaa$_{(12)}$, Xaa$_{(17)}$, and Xaa$_{(18)}$ are independently Nal(1), His, Phe, Trp, Tyr, Pro, Gln, or Met.

18. Paragraph beginning at line 8 of page 97 has been amended as follows, with bold font indicating added text and brackets surrounding stricken-out text indicating deleted text:

Table I

Relative affinities of bp1-16 variants measured by ELISA or BIAcore™(*) inhibition assays

bp1-16 Variant	Peptide Sequence	Fold potency reduction IC_{50}(mut)/IC_{50}(bp1-16)
bp1-16	CRAGPLQWLCEKYF (SEQ ID NO:37)	-1-
bp1-29	CRAAPLQWLCEKYF (SEQ ID NO:38)	50
bp1-30	CRAGALQWLCEKYF (SEQ ID NO:4)	1.5
bp1-31	CRAGRLQWLCEKYF (SEQ ID NO:5)	2.0
bp1-34	CRAGNLQWLCEKYF (SEQ ID NO:6)	3.1
bp1-32	CRAGPRQWLCEKYF (SEQ ID NO:39)	>1000
bp1-36	CRAGP[~~L~~]XQWLCEKYF (SEQ ID NO:7), where the underlined [~~L~~]**X** is Nle	6.9
bp1-26	CRAGPLQWRCEKYF (SEQ ID NO:40)	>570
bp1-37	CRAGPLQW[~~L~~]XCEKYF (SEQ ID NO:8), where the underlined [~~L~~]**X** is Nle	1.7
bp1-22	CRAGPLQRLCEKYF (SEQ ID NO:9)	3.3*
bp1-23	CRAGPLQ[~~A~~]XLCEKYF (SEQ ID NO:10), where the underlined [~~A~~]**X** is Nal(1)	4.8*
bp1-24	CRAGPLQHLCEKYF (SEQ ID NO:11)	7.5

19. Paragraph beginning at line 16 of page 107 has been amended as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

An improved consensus sequence for IGFBP-1 binding peptides is expected therefore to be:

$Xaa_{(1-4)}CysXaa_{(6)}Xaa_{(7)}GlyXaa_{(9)}$~~[Leu]~~**Xaa**$_{(10)}Xaa_{(11)}Xaa_{(12)}$~~[Leu]~~**Xaa**$_{(13)}CysXaa_{(15)}$ $Xaa_{(16)}Xaa_{(17)}Xaa_{(18)}$ (SEQ ID NO:1), wherein $Xaa_{(1-4)}$ is absent or is between 1 and 4 amino acids of any kind, $Xaa_{(6)}$, $Xaa_{(7)}$, $Xaa_{(9)}$, $Xaa_{(11)}$, $Xaa_{(15)}$, and $Xaa_{(16)}$ are independently any amino acid, **Xaa$_{(10)}$ and Xaa$_{(13)}$ are independently Leu or Nle,** and $Xaa_{(12)}$, $Xaa_{(17)}$, and $Xaa_{(18)}$ are independently Nal(1), His, Phe, Trp, Tyr, Pro, Gln, or Met. As noted in Example 1, truncation of the amino-terminal 4 residues ($Xaa_{(1-4)}$) has only a small effect on activity, giving a shorter consensus that still retains binding:
$CysXaa_{(6)}Xaa_{(7)}GlyXaa_{(9)}$~~[Leu]~~**Xaa**$_{(10)}Xaa_{(11)}Trp$~~[Leu]~~**Xaa**$_{(13)}CysXaa_{(15)}Xaa_{(16)}Xaa_{(17)}Xaa_{(18)}$ (SEQ ID NO:3).

20. Paragraph beginning at line 12 of page 110 has been amended as follows, with bold and underlining font indicating added text and brackets surrounding stricken-out text indicating deleted text:

Table VI

Peptide sequences for *E. coli* biosynthesis

Construct	Peptide sequence
bp1-625-Z	GQQSCAAGPLQWLCEHYFSTYGRGGGSGGAQHDEAVDNKFNKE QQNAFYEILHLPNLNEEQRNAFIQSLKDDPSQSANLLAEAKKLN DAQAPNVDMN (SEQ ID NO:~~[30]~~ **51**)
bp1-625	GQQSCAAGPLQWLCEHYFSTYGR (SEQ ID NO:29)

In the Claims:

Claims 1-26, 45 and 47-51 have been cancelled.

CLEAN SET OF PENDING CLAIMS

27. A constrained helical peptide comprising a sequence of nine amino acid residues having a first terminal residue and a second terminal residue, wherein said residues flank an internal sequence of seven amino acids and have side-chains covalently bonded to each other to form a locking moiety and thereby constrain the peptide.

28. The peptide of claim 27 wherein the internal sequence is $Xaa_{(7)}$LeuAla$Xaa_{(10)}Xaa_{(11)}Xaa_{(12)}Xaa_{(13)}$ (SEQ ID NO:31), wherein $Xaa_{(7)}$, $Xaa_{(11)}$, $Xaa_{(12)}$, and $Xaa_{(13)}$ are independently Nal(1), His, Phe, Trp, Tyr, Pro, Gln, or Met, and $Xaa_{(10)}$ is any amino acid.

29. The peptide of claim 28 wherein the first and second terminal residues are independently Asp or Glu residues.

30. The peptide of claim 29 wherein the first and second terminal residues are Glu residues.

31. A peptide comprising the following sequence: $Xaa_{(1-4)}Xaa_{(5)}Xaa_{(6-7)}$ProLeuGlu$Xaa_{(11)}$LeuAla$Xaa_{(14)}Xaa_{(15)}Xaa_{(16)}Xaa_{(17)}$ Glu$Xaa_{(19)}$ (SEQ ID NO:32), wherein $Xaa_{(1-4)}$ is absent or is between 1 and 4 amino acids of any kind; $Xaa_{(5)}$ is any amino acid, $Xaa_{(6-7)}$ is absent or is between 1 and 2 amino acids, $Xaa_{(14)}$ and $Xaa_{(15)}$ are independently any amino acid, $Xaa_{(11)}$ and $Xaa_{(16)}$ are independently Nal(1), His, Phe, Trp, Tyr, Pro, Gln, or Met, $Xaa_{(17)}$ is absent or is 1-napthyl-Ala, His, Phe, Trp, Tyr, Pro, Gln, or Met, and $Xaa_{(19)}$ is absent or is Gly.

32. The peptide of claim 31 wherein $Xaa_{(1-4)}$ is absent and an acetyl group is attached to $Xaa_{(5)}$.

33. The peptide of claim 31 wherein the Glu residues in SEQ ID NO:32 are joined by forming amides with 1,5-diaminopentane.

34. The peptide of claim 31 wherein C-terminal to the C-terminal $Xaa_{(19)}$ is the sequence $Xaa_{(20)}$ThrTyr, wherein $Xaa_{(20)}$ is any amino acid.

35. The peptide of claim 34 wherein $Xaa_{(20)}$ is Ala, Ser, Gln, Asp, Glu, or Lys.

36. The peptide of claim 31 comprising the following sequence: $Xaa_{(5)}Xaa_{(6-7)}$ProLeuGlu$Xaa_{(11)}$LeuAla$Xaa_{(14)}Xaa_{(15)}Xaa_{(16)}Xaa_{(17)}$GluGly (SEQ ID NO:33), wherein $Xaa_{(6-7)}$ is two amino acids.

37. The peptide of claim 31 wherein $Xaa_{(5)}$ is Arg.

38. The peptide of claim 31 wherein $Xaa_{(6-7)}$ is absent or is AlaGly.

39. The peptide of claim 31 wherein $Xaa_{(11)}$ is Trp.

40. The peptide of claim 31 wherein $Xaa_{(14)}$ is Glu.

41. The peptide of claim 31 wherein $Xaa_{(15)}$ is Lys.

42. The peptide of claim 31 wherein $Xaa_{(16)}$ is Tyr.

43. The peptide of claim 31 wherein $Xaa_{(17)}$ is Phe.

44. The peptide of claim 31 comprising one of the following sequences: ArgAlaGlyProLeuGluTrpLeuAlaGluLysTyrGluGly (SEQ ID NO:34); ArgProLeuGluTrpLeuAlaGluLysTyrPheGlu (SEQ ID NO:35); or ArgAlaGlyProLeuGluTrpLeuAlaGluLysTyrPheGlu (SEQ ID NO:36).

46. The peptide of claim 31 that contains 10-60 amino acids.